DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M3430

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail - Return Receipt Requested

March 3, 2000

And by Facsimile Transmission

CBER - 00 - 013

**Warning Letter**

James M. Wilson, M.D., PH.D., Director
Institute for Human Gene Therapy
204 Wistar Institute / University of Pennsylvania
3601 Spruce Street
Philadelphia, Pennsylvania 19104-4268

Dear Dr. Wilson:

During an inspection conducted from November 30, 1999, to January 19, 2000, Mr. Mike Rashti, an investigator from the Food and Drug Administration (FDA) Philadelphia District Office, and Dr. Thomas Eggerman, a Medical Officer from the FDA Center for Biologics Evaluation and Research (CBER), met with you to review your activities as the sponsor of research with an investigational adenovirus vector expressing the ornithine transcarbamylase (OTC) gene. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational new drugs.

- FDA has reviewed your firm's letter dated February 14, 2000, in which you responded to the Form FDA 483 - List of Inspectional Observations ("Observations") issued to you at the end of the inspection. Your firm's response purports to explain the source of some of the deviations and proposes corrective actions. Our comments regarding your explanations will be addressed below. Questions designated with "→→" indicate that we request a response and additional information.

As the Director of the Institute for Human Gene Therapy (IHGT), you are responsible for ensuring that IHGT fulfilled all of its sponsor obligations. This letter addresses your duties as the sponsor of research with an investigational vector. You also participated as a Co-Investigator on the OTC deficiency (OTCD) study. Your activities as a clinical investigator will be discussed in a separate letter.

Based on information obtained during the inspection, we have determined that you have failed to fulfill the obligations as the sponsor of studies with investigational products, and violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published under Title 21, Code of Federal Regulations (CFR), Parts 312, 50, and 56. The applicable provisions of the CFR are cited for each violation.

**1. IHGT failed to maintain an effective IND (Investigational New Drug application) with respect to the investigations. [ 21 CFR § 312.50 ].**

**A. As sponsor, you failed to submit protocol amendments to FDA before study revisions were implemented. [ 21 CFR § 312.30(b) and (e) ].**

i. You did not submit protocol version 1.0, dated November 4, 1996, to the IND. Subjects — through — were enrolled in your study under this protocol version during the period of April to July, 1997.

Your firm's response letter dated February 14, 2000, does not dispute Observation #1 regarding protocol version 1.0.

ii. In protocol amendment version 2.0 dated August, 1997, IHGT changed the inclusion criterion of serum ammonia from less than 50 micro molar (version 1.0) to less than 70 micro molar (in all later versions). Although the new criterion was listed in the body of the revised protocol, you did not identify this change on the summary list of protocol changes forwarded to FDA. Dozens of protocol changes were identified in the summary of changes, including other changes in the listing of inclusion and exclusion criteria in the section entitled "Participant Criteria." Yet, this important change was excluded.

Your response letter dated February 14, 2000, states "... FDA did not express any objection or concern with respect to the plasma ammonia level specified in version 2...." We reject this explanation for Observation #4. The result of your failure to disclose this revision in the summary of changes is that the this revision was obscured from FDA consideration. It is incumbent upon sponsors to provide complete and accurate information to FDA.

iii. There are two protocols designated as version 4.0. As sponsor, you failed to submit the July 17, 1998, protocol amendment version 4.0 to the IND as required by 21 CFR § 312.30(b)(1)(ii). This protocol amendment included the following significant changes in the design of the study:

| Protocol version 3.0 (November 1997) - Section 4.1.1 Research Design and Methods - | The amended protocol version 4.0 (July 17, 1998) - Section 4.1.1 Research design and Methods - |
|---|---|
| [ | [ |

]

]

The effect of this revision was to eliminate the need to add an additional subject if a mild (Grade I-II) reaction occurred.

In addition, the "Preface" list of protocol changes states that this protocol version contains "... modifications by the investigators after the enrollment of the third cohort." We note that the date of this protocol revision was *after* Subject --- was enrolled and experienced a Grade III adverse event as the first subject in cohort four.

Your firm's response letter dated February 14, 2000, does not dispute Observation #1 regarding protocol version 4.0 (July 17, 1998).

iv. You failed to submit the November 1, 1998, protocol amendment version 4.0 to the IND as required by 21 CFR § 312.30(b)(1)(ii). This protocol amendment included significant changes in the design of the protocol.

For the purpose of this letter, we compare the November 1, 1998, protocol version 4.0 to the protocol version 3.0 because the July 17, 1998, protocol version 4.0 was never submitted to the IRB for approval and, therefore, could not be implemented as required by 21 CFR § 312.30. The following items reflect significant changes in the design of the protocol:

a. The "Preface" list of protocol changes states that this protocol version lists "... modifications by the investigators after the enrollment of the third cohort" (emphasis added).

We note that the date of this protocol revision (November 1, 1998) was *after* Subjects [redacted] were enrolled and experienced Grade III adverse events in cohort four. This protocol revision was not submitted to the University of Pennsylvania Institutional Review Board (IRB) until January 11, 1999, after Subject [redacted] experienced Grade III adverse events as the fourth subject in cohort four.

b. Section 4.1.1 Research Design and Methods - was revised as follows:

| Protocol version 3.0 (November 1997) - Section 4.1.1 - | Protocol version 4.0 (November 1, 1998) - Section 4.1.1 |
| --- | --- |
| [redacted] | [redacted] |

The effects of these revisions include the following: (1) it became conditional rather than mandatory to add an additional subject to the cohort if one subject develops a mild toxicity (Grade I-II); (2) you eliminated the provision to put the study on hold if two subjects develop mild toxicity; (3) you eliminated the Grade III-IV stopping rule; and, (4) you removed the provision to stop the study if three subjects in a cohort developed high titer neutralizing antibodies. These protocol revisions reflect significant changes that affect the safety of study subjects.

c. Section 4.3 Completion/Termination of Study and Safety Monitoring - was revised as follows:

| Protocol version 3.0 (November 1997) - Section 4.3 - | Protocol version 4.0 (November 1, 1998) - Section 4.3 - |
|---|---|
| [ | [ |
| ] | ] |

The effects of these revisions include the following: (1) it became conditional rather than mandatory to add an additional subject to the cohort if one subject develops a mild toxicity (Grade I-II); (2) you eliminated the provision to put the study on hold if two subjects develop mild toxicity; (3) you eliminated the requirement to halt the study if Grade III or higher toxicity occurs; and, (4) you eliminated the requirement that the IRBs and FDA participate in the decision as to whether it is appropriate for the study to resume after a mild (Grade II) adverse event in two subjects. These protocol revisions reflect significant changes that affect the safety of study subjects.

Your firm's response letter dated February 14, 2000, does not dispute Observation #1 regarding protocol version 4.0 (November 1, 1998).

**B. You failed to incorporate agreed upon protocol changes into the protocol. [ 21 CFR § 312.30(b) and (e) ].**

i. IHGT did not incorporate the FDA's request to amend the protocol [redacted]. Your memorandum dated December 17, 1996 *(enclosed)* documents your telephone conversation with Dr. Thomas Eggerman, FDA Medical Officer. [redacted]

FDA's position on this matter was discussed during a telephone conversation between you and Dr. Eggerman on December 13, 1996. In that conversation, FDA requested that male subjects should have additional follow-up and blood draws, and you agreed to revise the protocol to reflect this discussion.

You failed to incorporate these revisions into the amended protocol versions 2.0 (dated August 1997), 3.0 (dated November 4, 1997), and both versions 4.0 (July 17, 1998, and November 1, 1998). Based on this information, we reject the explanation for Observation #7 offered in your firm's response letter dated February 14, 2000, that there was uncertainty about the limitation. Your explanation does not refer to the more recent discussion with FDA.

ii. Subjects [redacted] developed Grade III toxicities (liver enzyme elevations) that were attributed to risk factors in the patients' medical histories. In the submission to the IND dated January 13, 1999, you expressly agreed in writing to incorporate these risk factors in the exclusion criteria of the protocol for the subsequent subjects, but the subsequent protocol revisions failed to include these risk factors as exclusion criteria.

Your firm's response letter dated February 14, 2000, does not dispute Observation #12.

**C. As sponsor, you failed to immediately report the occurrence of adverse reactions in violation of your written agreement.**

In your letter to FDA dated December 4, 1996, you confirmed that one Grade III toxicity will stop the trial until discussed with FDA and that you would immediately notify FDA of adverse events. Nevertheless, you failed to immediately notify and consult FDA about the Grade III liver enzyme elevation in Subject — You subsequently enrolled Subject —, who also experienced a Grade III liver enzyme elevation. Again, you did not immediately notify and consult FDA of the adverse event experienced by Subject —

Your firm's response to Observation #13A does not accurately reflect your firm's discussions with FDA. After you notified FDA of the Grade III liver enzyme elevation in Subject —, FDA permitted you to enroll one more subject to determine if the significant liver function test increases were subject specific or dose related. You were told to submit the results of Subject —for FDA review, and you were told to add an additional subject to cohort four. You notified FDA by telephone regarding the Grade III liver enzyme elevation in Subject —. You submitted a summary of information about Subjects ——— to FDA in a written amendment two months after Subject — was administered the investigational vector.

In addition, the annual report dated March 2, 1999, failed to report that Grade III toxicities had occurred in cohort four. In fact, the annual report states, "

J The annual report did not include the results of all liver function tests, including the AST levels which were the Grade III toxicities in this cohort. You provided only the numeric average of laboratory results for ALT, alkaline phosphatase, hematocrit, and platelet count, which did not accurately portray the experience of these subjects. The annual report, therefore, misrepresented the true nature of the toxicities experienced by these four subjects.

We have the following additional comments about your firm's response to Observation #13A. To support your firm's decision to escalate the dose in a new cohort of subjects despite the adverse events, your response describes the Grade III toxicities experienced by Subjects ——— as transitory and "clinically non-significant." From FDA's perspective, these conclusions about the adverse events and your enrollment of subjects at the next higher dose level ignore your verbal agreement to obtain FDA concurrence before beginning a new cohort.

We reject your firm's explanation that your decision to not report the Grade III toxicities experienced by Subjects ——— to FDA "...was consistent with previous communications between IHGT and FDA...." The purpose of these reports was to evaluate the implications of the toxicities for subsequent subjects. There were no obvious pre-existing risk factors in Subjects ———— that could account for the adverse events experienced after the infusion of the investigational vector. Your actions demonstrate a disregard for the protocol stopping rules you had agreed to follow that were designed to protect the safety of study subjects.

D. **As sponsor, you failed to notify FDA in a written IND safety report of the findings from tests in laboratory animals that suggest a significant risk for human subjects.** Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. [ 21 CFR § 312.32(c)(1)(B), 21 CFR § 312.56(c) ].

IHGT did not submit the results of monkey study #98-63 in a timely manner. The study was conducted from October 27, 1998, to December 10, 1998, concurrent with the OTCD study. IHGT submitted a draft study report to FDA one year later, on October 27, 1999.

Your firm's letter dated February 14, 2000, agrees that "... study #98-63 should have been provided to FDA sooner." Your response also offers justifications for your actions. We reject your firm's explanations for the following reasons:

(1) Study #98-63 ended less than one month after human study cohort four was completed. The adverse events experienced by each of the four subjects in cohort four was similar to the liver damage experienced by the monkey infused with the vector used in the OTC human study. While several subjects had experienced thrombocytopenia, no subject had yet experienced clear disseminated intravascular coagulation (DIC) prior to the time the monkeys did. The fact that Subject — subsequently developed DIC confirms that, despite your assertion to the contrary, the toxicity experienced by the monkeys did have significant implications for the safety of the OTCD study. You had an affirmative obligation to notify FDA about these results so they could be evaluated.

(2) The protocol for monkey study #98-63 states that six animals were to be used in this study. Protocol amendment 001 states the following:
[

] The report your firm submitted to the IND includes the results of only three of these animals. Your firm's response

states that "... IHGT... fully intended to report the study and did so." In fact, you did not fully report the study. →→ Please explain the disposition of the other four animals.

(3) Your response states, "... the two monkeys that received the first- and second-generation vectors became severely ill and were euthanized." However, the individual animal tables submitted to FDA on October 27, 1999, [redacted] →→ Please explain this discrepancy.

(4) Your firm's response states, "The IRB approved the protocol for the clinical trial of [redacted] In fact, there was no IRB meeting held on August 30, 1999.

(5) The OTC Team meeting minutes document the discussion about study #98-63. The minutes read, in part: [redacted]

These statements indicate that the other monkeys who received the 001 vectors (one or more animals) did not survive. →→ Please explain how the non-survivors are not directly relevant to the human study underway at that time.

**E. You failed to revise the informed consent form when requested to do so by FDA.**

In FDA's letter dated June 13, 1996, you were requested to add additional information to the informed consent document, including an instruction that subjects were not to donate blood or gametes, and to describe the potential germ-line effects of gene therapy. You expressly confirmed in writing that you added the information not to donate blood or gametes to the consent form. You did not add such wording to the consent form submitted to the IRB at any time during the study. This information was important to adequately inform the potential study subjects whose consent was sought, and was required to adequately inform the potential study subjects.

**2. You failed to fulfill the general responsibilities of sponsors. [ 21 CFR 312.50 ].**

**A. The Institute for Human Gene Therapy (IHGT) lacks standard operating procedures (SOPs) to conduct a clinical study.**

Your firm's response letter dated February 14, 2000, agrees with this element of Observation #6. We acknowledge your firm's commitment to develop clinical trial SOPs by April 6, 2000. →→ Please submit the completed SOPs by this date to the address at the end of this letter.

**B. IHGT did not provide clinical investigators with the information they need to conduct an investigation properly.**

i. IHGT did not develop case report forms for use in this study. Case report forms are useful tools to ensure that all eligibility criteria are fulfilled before enrolling study subjects, to verify that all study procedures are performed at the appropriate time, and to document adverse events and measurements of efficacy. Case report forms are also useful to document the study personnel who perform study-related assessments. IHGT staff discussed the need for case report forms during an OTC Team meeting held before the start of cohort two.

Your firm's response to Observation #2 confirms that IHGT did not use an eligibility form when potential subjects were screened for the trial, and states the commitment to develop case report forms and an eligibility checklist for each clinical study.

ii. We have the following comments about Observation #3 regarding the eligibility checklists developed after the study was closed. Presuming that the checklists are complete and accurate, our review of the checklists shows that your staff were not able to retrospectively verify that each subject met each inclusion criterion before enrollment. The following are examples of incomplete information or information that indicates that the subject might not be eligible (this is not a complete listing):

a. Subject ' — Inclusion criterion (e) was not completed. Exclusion criteria (f)(8), (f)(9), (g), and (g)(5) were not completed.

b. Subject — · Inclusion criterion (l) was not completed. Exclusion criterion (c) is marked "?."

c. Subject [redacted]. Inclusion criterion (I) is marked with both a "?" and "✓" with no indication which entry is correct. Exclusion criterion (f)(4) is marked "?."

C. **IHGT did not ensure that the clinical investigators amended the informed consent document following the Grade III liver enzyme elevations experienced by each of the four subjects enrolled in the fourth cohort (Subjects [redacted]).** You failed to provide potential subjects with new information about the possible risks of participation since all of the subjects receiving a lower dose of the investigational vector experienced significant adverse events.

D. **IHGT does not have SOPs for the training of study staff, and does not have documentation that personnel are trained regarding the responsibilities of clinical investigators.**

We disagree with your firm's response to Observation #17. We expect that clinical investigators and clinical staff who are fully trained in Good Clinical Practices and in FDA regulations for human clinical trials would not have made the numerous errors that were documented in the inspection.

3. **As sponsor, you failed to select monitors. [ 21 CFR § 312.53(d) ].**

Although FDA recognizes that IHGT employs at least one individual who has the training and experience to monitor the progress of the investigations sponsored by your firm, this did not fulfill your obligations under the regulation.

Section 5.2 in protocol versions 2.0 and 3.0 states [redacted] However, the procedures of the Quality Assurance Unit are not defined. From the information available to FDA, it is not clear whether the QAU has the authority to monitor the study and to attempt to correct deficiencies. We conclude from the extensive deficiencies documented during the inspection that the QAU was not a functional entity because it lacked a meaningful influence over the clinical investigators to prevent or correct the deficiencies described in this letter and on the Form FDA 483.

In your firm's response letter dated February 14, 2000, you separated Observation #6 into two components; the second part will be addressed in item 4, below. Your firm's response states that IHGT "... has not implemented a formal mechanism for independently monitoring compliance with the numerous administrative requirements applicable to the OTCD study." You further describe how IHGT monitored the performance of protocol-required testing, the maintenance of complete and accurate records, the complete and timely communications with the IRB, and the execution of informed consent documents.

We reject your explanation that the informal processes IHGT used for monitoring were adequate for the OTCD study.

**4. You failed to review ongoing investigations. [ 21 CFR §§ 312.50 and 312.56 ].**

As sponsor, you failed to monitor the conduct of the OTCD study in that you did not assure and confirm that the participating clinical investigators fulfilled the responsibilities listed below. Effective monitoring should have prevented the following problems revealed by the inspection:

**A. You failed to ensure that only eligible subjects were enrolled.**

i. Subject — a male, was enrolled as the second subject in cohort six. This was a violation of your firm's agreement with FDA that male subjects could only be enrolled as the third subject in a cohort. You did not request FDA approval to deviate from this requirement.

Your response letter of February 14, 2000, states your belief that "... the communications between IHGT and FDA with respect to ordering of male and female patients were inconsistent...." Your response letter also states that FDA's permission to infuse male subject - as the second person in the cohort "... led the IHGT investigator to believe that FDA did not believe it was necessary to limit males to the third position in the cohort."

We reject your firm's response to Observation #8. As described in item 1B(i) above, your memorandum dated December 17, 1996, acknowledges FDA's request that [redacted] FDA agreed to permit you to enroll male Subject 016 as the second subject in cohort five after an evaluation of the subject's unique disease characteristics. You had no basis to assume that FDA would agree to permit enrollment of Subject — as the second subject in cohort six.

ii. Under protocol version 1.0 (November 4, 1996), all subjects must have plasma ammonia levels less than 50 micro molar at the time of the study. The following subjects, who comprise all of cohort one, had plasma ammonia levels greater than 50 micro molar in the immediate pre-infusion period, and thus appear not to have met this inclusion criterion:

a. Subject — - 63 and 58 micro molar on day —

b. Subject — - 121 and 70 micro molar on day —

c. Subject — - 51 micro molar on day — 52 micro molar on day —

→→ Please provide documentation of the timing of the $N^{15}$ study in relation to the serum ammonia tests for all subjects in the OTCD study. →→ Please describe how you determined that these subjects were eligible for the study.

iii. Under protocol versions 2.0, 3.0, and 4.0 (July 1998 and November 1998), subjects must have a plasma ammonia level less than 70 micro molar. Subject —, had plasma ammonia levels greater than 70 micro molar in the immediate pre-infusion period, and thus did not meet this inclusion criterion. The serum ammonia levels were 114 micro molar on day— and 91 and 113 micro molar on day —

We reject your firm's response to the specific case of Subject— as Observation #5, in the letter dated February 14, 2000, for the following reasons:

(1) Protocol version 0 (dated April 16, 1996) and version 1.0 (dated November 4, 1996) state the following; "

] (emphasis added). Subject —— were enrolled under protocol version 1.0. This specific wording was deleted in all later versions of the protocol. Your firm's response dated February 14, 2000, appears to disregard the wording in protocol versions 0 and 1.0.

(2) Your response explains that clinical investigators could "exercise clinical judgment" "in the absence of protocol requirements establishing a precise schedule for ammonia level testing." During the course of the study, if IHGT determined that the plasma ammonia test schedule was not clearly specified [which FDA believes was appropriately described in (1) above, and in

protocol Section 7 - Schedule of Events], then you should have either revised the protocol to clarify the ammonia inclusion criterion, or, alternately, established a consistent approach for assessing whether prospective subjects should be included in the study.

(3) For the four subjects listed above, IHGT had the opportunity to defer the infusion in order to determine whether the serum ammonia level would decrease, but instead, in each case IHGT decided to proceed with the infusion.

(4) Serum ammonia levels are critical in the screening of potential subjects. Since a subject's condition may change suddenly in OTCD, the clinically most relevant levels are those measured closest to the time of vector administration. It is not appropriate to rely on serum ammonia levels measured weeks before the infusion of the investigational vector, especially when ammonia values are available significantly closer to the time of the administration.

(5) Your firm's response cites the transitory and variable nature of serum ammonia levels. →→ Please explain how many tests were performed, over how many days, during the screening assessment of each study subject, which served as the basis for your decision to enroll each subject. →→ Please provide all screening ammonia levels test results for each subject who was screened.

**B. You failed to ensure that the protocol was followed.**

i. The clinical investigators did not perform the following protocol-required tests during the hospitalization phase of the protocol (this is not a complete list):

a. Subject —— Baseline CBC and differential count at day — we note your explanation that the sample was not properly labeled and was therefore not analyzed. A pre-infusion CBC should have been performed on days ——. On the day of the infusion, laboratory testing revealed the following abnormal laboratory results: red cell count, hemoglobin, hematocrit, and differential count. Pre-infusion testing could have revealed pre-existing abnormalities indicating that the study potentially exposed the subject to additional risks. Decreased blood cell counts were seen in previous subjects, so these baseline measurements were critical to evaluate the safety of the study. Subject—— subsequently developed

a Grade III hemoglobin value and other abnormalities that continued at least through study day — . →→ Please submit copies of laboratory slips for all CBC results during the immediate pre-infusion period for this subject.

b. Subject — Creatinine, BUN, PT/PTT, CBC, and platelet count on pre-infusion day — No baseline laboratory tests were performed.

c. Subjects — You did not perform the protocol-required tests on days — Instead, the tests were performed from 13 to 19 days before the infusion of the investigational vector.

Your firm's response letter describes your Institutional policy regarding processing of manual differential counts. →→Please describe what special arrangements your firm will make to ensure that protocol-required safety measurements will be performed during the hospitalization period.

ii. The clinical investigators did not perform the following protocol-required tests during the post-hospitalization / follow-up phase of the protocol (this is not a complete list):

a. Subject . GGT on days — This subject was discharged with a Grade III abnormality of GGT and was never retested to determine if or when the value returned to normal.

b. In view of the laboratory abnormalities observed in this study related to liver function and blood counts, it was very important to conduct the protocol-required laboratory tests after discharge from the University of Pennsylvania. No follow-up laboratory tests were performed for the following subjects (this is not a complete list):

| TEST | Day — | Day — | Day — | Day — |
|---|---|---|---|---|
| Differential count | Subjects — | Subjects — | Subjects — | Subjects — |
| Liver function test | — | — | — | — |
| CBC | — | — | — | — |

→→ Please provide copies of all available data and the supporting laboratory slips for the required laboratory tests (liver function tests, CBC, differential count, platelet count) for all subjects for days [redacted] If the tests were not performed, your response should so state.

Your firm's response letter dated February 14, 2000, states that "...IHGT monitored all aspects of the OTCD study—including in particular those bearing on patient safety—by...constantly reviewing and analyzing test results and clinical assessments for individual patients and for each cohort...each patient's progress was continuously monitored throughout the trial by IHGT...Exhaustive clinical assessments of each patient were performed throughout the patient's in-hospital stay and follow-up period." (IHGT response to Observation #6).

Your firm did not complete the scheduled laboratory assessments according to the protocol. We do not agree with your firm's position that laboratory safety assessments were adequate. Your firm's amendments to the IND dated December 4, 1996, April 9, 1997, June 17, 1997, and September 15, 1997, describe how your firm planned to interact with the physicians near the subjects' residences to obtain the follow-up laboratory assessments following discharge from the Hospital of the University of Pennsylvania.

We conclude that your firm did not exert due diligence to ensure that the follow-up tests were performed according to the protocol. →→ Please explain what information you provided to the subjects' physicians to inform them of the testing required by the protocol, and why the follow-up testing was not conducted according to the protocol. Provide documentation of your contacts with the physicians.

C. **You failed to ensure that complete and accurate records were maintained.**

i. During the FDA inspection, you were unable to provide documentation of the results of the day [redacted] screening serum ammonia levels for Subjects [redacted]

Your firm's response letter dated February 14, 2000, for Observation #15, states that you will intend to submit these results to FDA. →→ In addition to the baseline test results, please include a copy of the supporting laboratory slips. →→ Please explain whether the screening laboratory assessments were processed by

the University of Pennsylvania Hospital central laboratory, or by laboratories local to the subjects. →→ Please explain why these results were not available at the time of the inspection.

ii. The laboratory test flow sheets prepared for each subject do not accurately record all the testing that was conducted. The following examples are illustrative:

a. Subject — Differential count on day —

b. Subject — Creatinine and BUN on day —

c. Subject — PT/PTT on day – differential count on day —

iii. It is misleading to characterize the laboratory tests performed weeks before the infusion as day— results; see item 4B(i)(c), above. Even though the actual date of the testing is included in some tables and charts submitted to FDA, you should correctly identify the day of testing relevant to the infusion of the test article.

D. **You failed to ensure that the clinical investigators provided complete and accurate information to the IRB,** including protocol revisions (with all revisions highlighted to ensure proper consideration of the proposed changes) and adverse event reports.

Your firm's letter of February 14, 2000, agrees with Observation #13B, and states that IHGT should have complied with the additional reporting requirements included in your protocol.

E. **You failed to ensure that the informed consent of patients was properly documented.**

The process of describing the study to prospective subjects was not well documented. In the examples listed in Observation #10, the signature dates reflect that the witness and/or clinical investigator signed the consent forms on different dates.

Your firm's response to Observations #9 and #10 generally describes the process used to conduct the informed consent discussion with the prospective subjects. After discussing the study with the study staff, subjects were allowed to take the consent forms for further review. FDA agrees that this is important in studies that are especially complicated. We would anticipate, however, that neither the subject nor study staff

would sign the consent form until after a subsequent meeting to answer any unresolved or new questions. Another option is to have the subject sign a clean copy of the consent form during the subsequent interview.

The absence of a witness signature or clinical investigator signature from a consent form indicates that the individual was not present during the informed consent interview.

We reject your firm's explanation for Observation #10E.

5. **As sponsor, you failed to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. [ 21 CFR § 312.57(a) ].**

IHGT cannot account for all inventories for study drug lots [redacted]

Your response letter dated February 14, 2000, acknowledges that Observation #18 is correct and states that corrections were implemented.

→→ Please submit the following data, in tabular form by subject, along with a copy of the supporting laboratory printouts or assay calculations. These analyses are identified in protocol version 4.0 (November 1998). Please submit all results for all assays performed, and so state if the tests were not performed.

A. Results of "efficacy" (gene activity) testing: study days [redacted] and [redacted]

B. Blood testing for amino acids: study days [redacted]

C. Urine analysis for orotic acid: study days [redacted]

D. Blood testing for $^{15}N$ study: study days [redacted]

E. CTL assay: study days [redacted] Please report the day [redacted] results when they be come available.

F. Proliferation assay: study days [redacted] Please report the day [redacted] results when they be come available.

G. Neutralizing antibody assay: study days [redacted] Please report the day [redacted] results when they be come available.

Your firm's response letter proposes several follow-up actions, including the preparation of standard operating procedures (SOPs) and the transfer of some sponsor obligations to a contract research organization. As part of your response to this letter, please provide the anticipated time frames in which the SOPs will be implemented, and provide more detailed information about the implementation of your suggested actions.

We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations to prevent the recurrence of similar violations in future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations.

Your firm's INDs remain on clinical hold. We request that your firm refrain from submitting new INDs to FDA until SOPs have been developed and reviewed by FDA, and other corrective actions have been implemented.

Please send your written response to:

Patricia Holobaugh (HFM-650)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Philadelphia District Office, U.S. Customhouse, 2nd and Chestnut Streets, Room 900, Philadelphia PA 19106.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure

IHGT memorandum dated December 17, 1996

cc: Dr. Judith Rodin, Ph.D., President
University of Pennsylvania
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Philadelphia, PA 19104-6380

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